

(Amended) Human Methionine Synthase Reductase: Cloning, and Methods for Evaluating Risk of, Preventing, or Treating Neural Tube Defects, Cardiovascular Disease, Cancer, and Down's Syndrome.

In the Claims

Replace claims 1-3, and 5 with the following amended claims that have been re-written in clean form. Please cancel claim 4 without prejudice.

B¹
1. (Amended) A method of preventing cancer, cardiovascular disease, Down's syndrome, or a neural tube defect in a subject, said method comprising administering to said subject a compound selected from the group consisting of a protein, a small molecule, and an antisense nucleic acid molecule; wherein said compound modulates methionine synthase reductase biological activity in said subject in an amount sufficient to prevent said cancer, cardiovascular disease, Down's syndrome, or neural tube defect.

2. (Amended) A method of preventing Down's syndrome, said method comprising administering to the subject a therapeutically effective dose of a metabolite or cofactor selected from the group consisting of folate, cobalamin, S-adenosyl methionine, betaine, and methionine.

3. (Amended) The method of claim 1, 2, or 26, wherein said subject has been diagnosed as having a mutation or polymorphism in methionine synthase reductase.

B²
5. (Amended) The method of claim 1, 26, or 28, wherein said cardiovascular disease is premature coronary artery disease.

Add the following new claims 22-34.

22. (New) The method of claim 1, wherein said compound modulates the level of methionine synthase reductase protein or mRNA in said subject.

23. (New) The method of claim 1, wherein said compound modulates the amount of methionine in said subject.

24. (New) The method of claim 1, wherein said compound increases said methionine synthase reductase biological activity.

25. (New) The method of claims 1, wherein said compound decreases said methionine synthase reductase biological activity.

26. (New) A method of treating or preventing cardiovascular disease, said method comprising administering to the subject a therapeutically effective dose of a metabolite or cofactor selected from the group consisting of S-adenosyl methionine, betaine, and methionine.

27. (New) A method of preventing disease in a test subject with an above normal or below normal level of methionine synthase reductase biological activity, said method comprising:

(a) detecting an MTRR mutation or polymorphism that results in altered methionine synthase reductase biological activity; wherein said detection step comprises analyzing a methionine synthase reductase nucleic acid from one or more test subjects selected from the group consisting of a mammal; a potential parent, either male or female; a pregnant mammal; a developing embryo; and a developing fetus; and

(b) administering a therapeutically effective dose of a metabolite or cofactor selected from the group consisting of folate, cobalamin, S-adenosyl methionine, betaine, and methionine to said test subject.

28. (New) The method of claim 27, wherein said disease is a neural tube defect, cardiovascular disease, or Down's syndrome.

29. (New) The method of claim 27, wherein said detection step comprises:

B³ (a) amplifying a methionine synthase reductase nucleic acid in a sample obtained from said test subject; and

(b) sequencing said amplified methionine synthase reductase nucleic acid to detect the presence or absence of a mutation or polymorphism in said methionine synthase reductase nucleic acid.

30. (New) The method of claim 29, wherein said amplification step is performed using one or more primers selected from the group consisting of SEQ ID NO: 3-20.

31. (New) The method of claim 27, comprising administering said metabolite or cofactor to both (i) said pregnant mammal and (ii) said embryo or said fetus.

32. (New) The method of claim 2 or 27, wherein said cobalamin is administered to a subject having a low serum cobalamin level.

33. (New) A method of treating cancer, cardiovascular disease, or a neural tube defect in a subject, said method comprising administering to said subject a compound selected from the group consisting of a protein, a small molecule, and an antisense nucleic